The 1,3-dimethyl-4-*n*-propylbenzene is largely rearranged by aluminum chloride at 100° for four hours to yield 1,3-dimethyl-5-isopropylbenzene. After heating at 85–90°, the trialkyl fraction is a mixture, and at 55° the trialkyl fraction is mainly unchanged 1,3,4 hydrocarbon.

The 1,3-dimethyl-4-*n*-propylbenzene was prepared from *m*-xylene and cyclopropane with aluminum chloride as the catalyst, and by the reduction of 4-propionyl-*m*-xylene.

The 1,3-dimethyl-5-isopropylbenzene was obtained from *m*-xylene and isopropyl chloride, *n*-propyl formate, and *n*-propyl chloride with aluminum chloride as the catalyst.

The formation of the 4-*n*-propyl hydrocarbon from *m*-xylene and cyclopropane and the 5-isopropyl hydrocarbon from *m*-xylene and *n*-propyl formate support the view of Smith and Perry that a 1,3,4 hydrocarbon is the initial product of the reaction when *m*-xylene is alkylated in the presence of aluminum chloride.

COLUMBIA, MISSOURI RECEIVED OCTOBER 5, 1939

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

The Hydrogenation of Coumarin and Related Compounds

BY PETER L. DE BENNEVILLE AND RALPH CONNOR

γ-Valerolactone at 250° and 100–200 atmospheres of hydrogen over a copper chromite catalyst has been reported[1] to give pentanediol-1,4, the product expected from an ester under these conditions, and a small amount of hydrogenolysis product, pentanol-1. Over nickel, however, γ-butyrolactone and γ-valerolactone gave[2] 9% of tetrahydrofuran and 17% of α-methyltetrahydrofuran, respectively. These seem to be the only known examples, except in cases where other functional groups complicate the reactions, of the formation of ethers and also of the attack of an ester group in the presence of a nickel catalyst. Apparently no other γ-lactones and no δ-lactones have been investigated under these conditions.

The products obtained by the hydrogenation of coumarin and certain related compounds are shown in the flow sheet (Table I). Over copper chromite, the behavior of coumarin was like that of any α,β-unsaturated ester. The formation of dihydrocoumarin (II) at 140–160° was shown by the pressure drop but the hydrogenation was not interrupted to permit its isolation. At 250° there was obtained a good yield of the product expected from a normal ester hydrogenation, γ-(*o*-hydroxyphenyl)-propyl alcohol (V).

Dihydrocoumarin (II) was isolated from the hydrogenation of coumarin over Raney nickel at 100°. In hydrogenations at higher temperatures dihydrocoumarin was not isolated but was formed quantitatively, as shown by the hydrogen absorption, before any subsequent reaction occurred. At 200–250° the main reactions which occurred over Raney nickel were saturation of the benzenoid ring, giving octahydrocoumarin (III), and conversion of the lactone to the cyclic ether, hexahydrochroman (IV). Pure octahydrocoumarin was obtained in 50–55% yields by carrying out the hydrogenation at 200° and interrupting the reaction before the absorption of hydrogen had ceased.[3] Under these conditions 10–15% of hexahydrochroman was formed. Higher yields (up to 35%) of the latter product were obtained by using a relatively long reaction period at 250°.

Since the formation of ethers from esters over nickel is by no means a common reaction, it is of some interest to determine the intermediates in the formation of hexahydrochroman from coumarin. Three possible mechanisms are shown by broken lines in Table I and none of these may be definitely eliminated on the basis of the facts now available. Path (c) agrees with the observation that IV is the sole product obtained by the hydrogenation of III under these conditions. This also agrees with the results previously mentioned with γ-butyrolactone and γ-valerolactone except that the yield of ether from coumarin was

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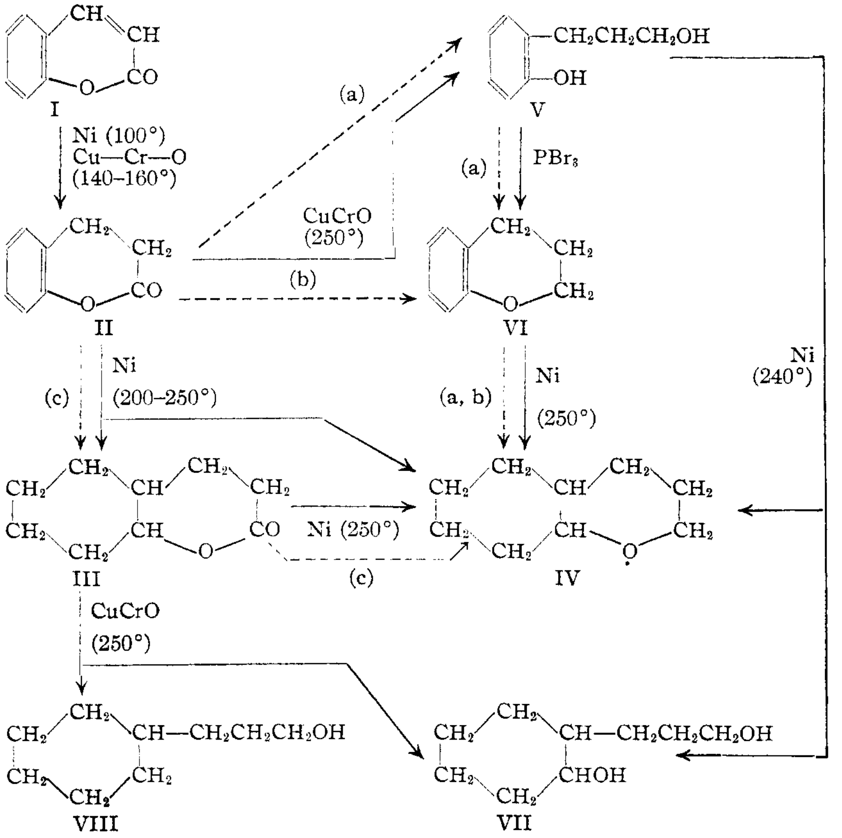
(1) Adkins, "Reactions of Hydrogen, etc.," University of Wisconsin Press, Madison, Wisconsin, 1937, p. 105.

(2) Ref. 1, p. 77.

(3) A plot of time against pressure showed a definite change in slope which seemed to mark the best time to interrupt the reaction. At 250° this point was not observed readily and, while good yields (60–70%) of the octahydrocoumarin fraction were obtained, the refractive index of the product showed that it contained unreacted dihydrocoumarin.

TABLE I

PRODUCTS FROM THE HYDROGENATION OF COUMARIN AND RELATED COMPOUNDS[a]



[a] Full lines refer to reactions described in Table II and the experimental part and broken lines to the possible mechanism for the formation of IV from II over nickel.

TABLE II

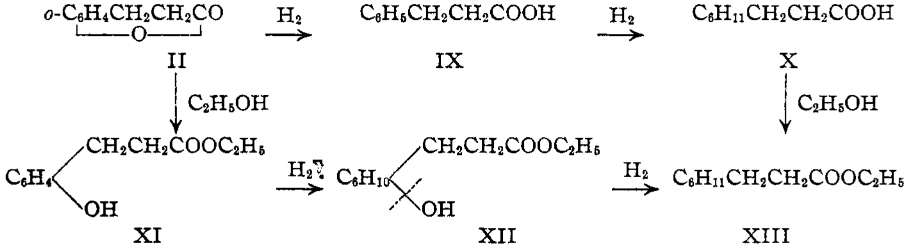
HYDROGENATION DATA[a]

				Catalyst, g.			% Products (see Table I)							
Compd.	Moles	Time, hrs.	Solvent	Ni	Cu-Cr	Temp., °C.	II	III	IV	V	VII	VIII	XIII	Polymer
I	0.2	8	C_2H_5OH	5	..	200	..	32	31	..	..	..	7	27
I	.2	4	C_2H_5OH	5	..	250	..	41	27	..	..	..	13	6
I	.2	3	C_7H_{14}	5	..	205	..	53	13	..	..	..	..	10
I	.2	0.3	C_7H_{14}	5	..	250	..	58[b]	9	..	..	..	..	11
I	.2	13.5	C_7H_{14}	5	..	250	..	19[c]	35	..	..	..	..	27
I	.2	0.5	$(C_2H_5)_2O$	5	..	100	90	..	..	..	..	..	..	..
I	.5	0.7	C_2H_5OH	..	5	250	..	..	..	90	..	..	..	..
I	.7	1.5	...	..	10	250	..	..	..	83	..	..	..	..
III	.08	6	C_7H_{14}	5	..	250	..	..	57[d]	..	..	..	..	..
III	.06	4.5	C_7H_{14}	..	3	250	..	..	..	..	50[d]	11	..	..
V	.13	2	C_2H_5OH	4	..	240	..	..	40	..	37	..	..	..
VI	.05	6	C_2H_5OH	2.5	..	250	..	..	41[d]	..	..	..	..	..
$C_6H_5(CH_2)_3OH$	.11	2	C_2H_5OH	3.3	..	220	..	..	..	..	..	86	..	..

[a] The reactions were carried out under a hydrogen pressure of 100–200 atm. [b] According to the refractive index (n^{25}_D 1.5025) this fraction probably contained some dihydrocoumarin (n^{25}_D 1.5541). [c] According to the refractive index (n^{25}_D 1.4728) this fraction probably contained some β-cyclohexylpropionic acid (n^{20}_D 1.4634). [d] Apparently the starting materials were converted completely to the products named but recovery was low because of the high mechanical loss in distilling small amounts of material.

considerably higher than from the γ-lactones. Path (b) seems the least probable of the three in view of the fact[4] that the structure $-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\mathrm{O}-\mathrm{Aryl}$ is not converted to $-CH_2O-$Aryl under these conditions. Mechanism (a) represents the attack of the ester group over nickel proceeding according to that over copper chromite. The fact that IV was formed by the hydrogenation of pure V and of pure VI agrees with this mechanism. The formation of IV from V is, however, of some interest since it appears to be the first case of ring closure by dehydration under these conditions. It is noteworthy that nickel apparently catalyzes the ring closure, since no ethers were formed from γ-(*o*-hydroxyphenyl)-propyl alcohol and γ-(2-hydroxycyclohexyl)-propyl alcohol under conditions that were similar except that the catalyst was copper chromite.

The results of typical hydrogenations are reported in Table II. Certain by-products mentioned may require explanation. According to the behavior of esters of phenol,[4] it would be expected that dihydrocoumarin would give some β-phenylpropionic acid (IX) and that β-cyclohexylpropionic acid (X) would be the final product from this reaction. Indications of the presence of the acid were obtained (Table II) in prolonged hydrogenations in the complete absence of alcohol. However, this acid and the saturated lactone (III) have boiling points so close that they could not be separated by distillation and the use of alkali was futile because of the pseudo acid character of III. Additional evidence for the formation of X was obtained by the identification of its more readily isolable ethyl ester (XIII) when alcohol was present.[5] It should be pointed out, however, that except for the analogy to the behavior of aryl esters,[4] there is no evidence to exclude the possibility that XIII was formed by the alcoholysis of dihydrocoumarin, followed by hydrogenation and hydrogenolysis of the hydroxy esters (XI and XII).



The material designated as "polymer" in Table II was formed in larger amounts at 250° and as the time of the hydrogenation was prolonged. It was a thick, slow-flowing, non-distillable material which did not crystallize[6] but remained as the residue from the distillations. The yields of this material reported (Table II) were calculated from the total weight of the distillation residue and include the octahydrocoumarin which was present because of the hold-up of the fractionating column.

Since hexahydrochroman had not been made previously and since it had no reactive functions to facilitate a confirmation of its structure, it seemed necessary to prepare a sample of the material by a more orthodox method. This was done by the hydrogenation of chroman over nickel and the comparison of the physical properties of the two products to show that they were identical (Table III). The methods already described for the synthesis of chroman were not particularly satisfactory and as a matter of convenience a simple synthesis using coumarin as the starting material was devised. This method involved the hydrogenation of coumarin over copper chromite and treatment of the phenolic alcohol (V) with phosphorus tribromide.[7] The yields in these two steps were 90% and 87%, respectively.

These results show that coumarin may be converted to octahydrocoumarin, chroman or hexahydrochroman, depending on the conditions used. Because of the current interest in various natural products related to chromans and coumarins, the

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(4) This statement is based upon unpublished data of Wm. R. McClellan and will be described in detail in a forth-coming communication.

(5) Aside from the formation of this ester, no differences were noted in comparison of alcohol and methylcyclohexane as solvents.

(6) Treatment of III with sodium ethoxide gave a thick, sticky product which was presumably a polymeric ester. It seems likely that the high-boiling material formed during the hydrogenations was also composed of polymeric esters. A closer examination of this product wil lbe made.

(7) Semmler[8] prepared chroman from V by treatment with alcoholic hydrogen chloride in a sealed tube.

(8) Semmler, *Ber.*, **39**, 2856 (1906).

TABLE III

PHYSICAL CONSTANTS AND ANALYSES OF PRODUCTS

Compound	B. p. (obsd.), °C.	Mm.	n^{t}_{D}	t	d^{t}_{4}	MR$_D$ Calcd.	MR$_D$ Found
Octahydrocoumarin (III)[a]	144–146	16	1.4970	24°	1.0999	41.02	40.98
Hexahydrochroman (IV) (from coumarin)[b]	186–187	760	1.4714	22°	0.9536	41.00	41.07
Hexahydrochroman (IV) (from chroman)[b]	186–187	760	1.4718	22°	0.9533	41.00	41.25
Chroman (VI)	210–214	760	1.5462	23°	1.0575	39.52	40.13[c]
γ-(2-Hydroxycyclohexyl)-propyl alcohol (VII)[d]	185–186	35	1.4867	25°	1.0294	44.61	44.24
Ethyl β-cyclohexylpropionate (XIII)	105–113[e]	17	1.4480[e]	22°	....	...	...
γ-(o-Hydroxyphenyl)-propyl alcohol (V)	159–161[f]	5	Benzoate, m. p. 98.5–99.5°[f]				
γ-Cyclohexylpropyl alcohol (VIII)	105–106[g]	10	α-Naphthylurethan, m. p. 82–83°[g]				

[a] Saponification number: Calcd., 155; found, 154. Octahydrocoumarin was prepared by another method by Cook and Lawrence,[11] who reported that it boiled at 145° (10 mm.). Since they gave no other physical properties the identity of our product was confirmed by analysis for carbon and hydrogen. [b] The properties of hexahydrochroman from both sources are given, since their similarity serves as a confirmation of the structure assigned to these products. *Anal.* Calcd. for $C_9H_{16}O$: C, 77.07; H, 11.5. Found: C, 76.9, 76.7; H, 11.6, 11.7. [c] The molecular refraction (40.03) of chroman calculated from the results of Semmler[8] is also slightly above theoretical. [d] *Anal.* Calcd. for $C_9H_{18}O_2$: C, 68.4; H, 11.6. Found: C, 68.2, 68.2; H, 11.6, 11.6. [e] Saponification number: Calcd., 184; found, 182. Sabatier and Murat[12] had previously prepared this compound, b. p. 231° (760 mm.), n^{17}_{D} 1.452. The identity of our product was confirmed by comparison of the physical properties with a sample prepared by another method.[4] [f] Semmler[8] reported the boiling point of V as 177–178° (8 mm.) and the melting point of the benzoate as 99–100°. [g] A sample of γ-cyclohexylpropyl alcohol (VIII) was prepared by the hydrogenation of γ-phenylpropyl alcohol (Table II). The product (b. p. 116° (20 mm.), 218° (760 mm.)) gave an α-naphthyl urethan, m. p. 83–84°. A mixed melting point showed that this was identical with the derivative of the hydrogenolysis product reported above. *Anal.* Calcd. for $C_{20}H_{25}O_2N$: N, 4.49. Found, N, 4.31. Waser[13] reported the boiling point of VIII as 110–111° (11 mm.).

reactions described here are being extended to more complex derivatives.

Experimental Part

The coumarin used was purified by recrystallization from a mixture of benzene and ligroin (b. p. 70–90°). Certain samples of coumarin, presumably of natural origin, were hydrogenated to dihydrocoumarin over nickel but gave no further reaction at 200° and very slow reaction at 250°. Recrystallization removed the impurity responsible for this behavior and the results given in Table II were readily duplicated. For hydrogenation over copper chromite, Merck coumarin was used without recrystallization.

Hydrogenations.—The apparatus was similar to those already described[9] and was used in conjunction with a potentiometer-controller temperature-recorder. In the hydrogenations in which alcohol was the solvent, the commercial absolute grade was used. Raney nickel and copper chromite catalysts were made by the conventional methods.[10] The nickel catalyst was stored under alcohol but in the experiments in which it was desired to avoid the effects of alcohol, the catalyst was washed several times with ether and finally with methylcyclohexane. The hydrogenation products were dried over magnesium sulfate and distilled under reduced pressure through a 10-cm. Vigreux column or a Widmer column containing a spiral 11 cm. long. The results of the hydrogenations are given in Table II. Since most of the products did not contain reactive functions and could not be converted to solid derivatives, physical properties and analyses were important factors in identification. Fortunately, these were satisfactory for the elimination of any likely alternative structures. The data obtained are reported in Table III.

Chroman (VI).—A solution of 30.4 g. (0.2 mole) of γ-(o-hydroxyphenyl)-propyl alcohol (V) in 100 ml. of dry benzene was placed in a 500-ml. three-necked, round-bottomed flask fitted with a mechanical stirrer, a dropping funnel and a reflux condenser connected to a trap to dispose of hydrogen bromide. The solution was cooled in a water-bath at 5°, about 2 ml. of phosphorus tribromide added, and the mixture stirred until it had become warm enough for reaction to begin. The reaction flask was kept in the bath of cool water and the remainder of the phosphorus tribromide added slowly enough to avoid a violent reaction. A total of 40.7 g. (0.15 mole) of phosphorus tribromide was used and about one-half hour was required for its addition. The reaction mixture was stirred for an additional two hours, allowed to stand overnight and on the next morning refluxed for one-half hour on the steam-bath. After cooling, the flask was immersed in cold water and a solution of 24 g. (0.6 mole) of sodium hydroxide in 100 ml. of water added cautiously with stirring. This mixture was refluxed on the steam-bath with stirring for three hours and the layers separated. The aqueous layer was washed once with an equal volume of benzene and the combined benzene extracts washed with an equal volume of water. The benzene solution was dried over calcium chloride and distilled. The yield of chroman (VI) was 23.3 g. (87%), b. p. 125–130° (70 mm.). The product was a colorless liquid which contained traces of halogen,[14]

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(9) Ref. 1, p. 39.

(10) Ref. 1, pp. 13, 20.

(11) Cook and Lawrence, *J. Chem. Soc.*, 817 (1937).

(12) Sabatier and Murat, *Compt. rend.*, **156**, 752 (1913).

(13) Waser, *Helv. Chim. Acta*, **8**, 123 (1925).

(14) In this state the product was not hydrogenated over nickel but this treatment removed the impurity and the recovered chroman was readily hydrogenated by a second treatment over nickel (Table II).

and turned a straw color on standing. The physical properties of the product are given in Table III and exclude the possibility that it is the isomeric 2-methylcoumaran. The following properties have been reported for chroman[8] and 2-methylcoumaran,[15] respectively: b. p. 93.5° (8 mm.), 208–212°; n_D 1.54437 (20°), 1.5302 (25°); *d*, 1.0587 (20°), 1.028 (25°).

Omission of the treatment with alkali described above reduced the yields of chroman to 70–75%. None of the expected bromide was isolated but the chroman fraction contained large amounts of halogen. However, treatment of γ-(*o*-hydroxyphenyl)-propyl alcohol (V) with hydrobromic acid–sulfuric acid mixture as described[16] for lauryl bromide gave a 50% yield of chroman and 10% of what was probably γ-(*o*-hydroxyphenyl)-propyl bromide, b. p. 165° (23 mm.). The latter could not be purified, since hydrogen bromide was evolved slowly during distillation.

Summary

Products obtained by the hydrogenation of coumarin, or from its hydrogenation products, include dihydrocoumarin, octahydrocoumarin, chroman, hexahydrochroman and a substance believed to be a polymeric ester. Of especial interest is the conversion of δ-lactones and of a 1,5-glycol to cyclic ethers over Raney nickel.

PHILADELPHIA, PENNA. RECEIVED SEPTEMBER 15, 1939

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[15] Niederl and Storch, THIS JOURNAL, **55**, 4554 (1933).

[16] Gilman, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y., 1932, p. 27.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF YENCHING UNIVERSITY]

Ephedrine. III. Di-(α-hydroxyl-β-methylaminopropyl)-benzenes

BY STANLEY D. WILSON AND CHEN-TA CHANG

Although a large number of derivatives and homologs of ephedrine have been reported by numerous investigators, we can find no record of such derivatives with two α-hydroxyl-β-methylaminopropyl side chains. This paper reports the preparation of the meta and para compounds of this type. These compounds were prepared from the 1,3- and 1,4-dipropionylbenzenes, respectively, which we made from the corresponding phthalyl chlorides by modifications of Mixin's[1] method. According to this method the phthalyl chlorides were first converted into the diethyldiamides by treatment with diethylamine. These diethyl acid amides were then treated with ethylmagnesium bromide, which converted them into the desired dipropionyl compounds. In the first step Mixin employed ether as a solvent with the para compound but used benzene with the meta compound. The substitution of ether for the benzene in the case of the meta compound resulted in better yields and much greater ease in purification of the product. Mixin reports a yield of 25–30% in the second step from the Grignard reaction when he refluxed for four hours. We obtained yields of 35–40% by refluxing for nine hours.

The dipropionylbenzenes were next treated with bromine, which converted them into two new derivatives: 1,3- and 1,4-di-(α-bromopropionyl)-benzenes. When the bromo compounds were treated with methylamine they were converted into the corresponding di-(α-methylaminopropionyl)-benzenes which also have not been described previously. These amino compounds were then reduced by hydrogen in the presence of platinum to give the desired new ephedrines. The last three reactions have been employed in the preparation of the more normal types of ephedrine homologs by Späth and Göhring,[2] Hyde, Browing and Adams,[3] Wilson and Sun[4] and others.

The free base of the new para ephedrine was a thick oil but that of the meta compound was an amorphous solid. The salts of the para compound crystallized well and had high melting points, while the hydrochloride, sulfate, oxalate, and phosphate of the meta derivative were thick liquids, but the picrate was a somewhat gummy amorphous solid. This agrees with Koller's[5] finding, that salts of *p*-methoxyephedrine were crystalline and had melting points while the salts of *m*-methoxy-*p*-hydroxyephedrine were liquids. These compounds contain four asymmetrical carbons and their resolution into their optical isomers would be an interesting problem.

Experimental Part

Preparation of 1,4-Di-(α-bromopropionyl)-benzene.—8.41 g. of bromine was added gradually to 5 g. of 1,4-

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[1] Mixin, *Ann. Chim.*, **9**, 55 (1928).

[2] Späth and Göhring, *Monatsh.*, **41**, 319 (1920).

[3] Hyde, Browing and Adams, THIS JOURNAL, **50**, 2287 (1928).

[4] Wilson and Sun, *J. Chinese Chem. Soc.*, **2**, 243 (1934).

[5] Koller, *Monatsh.*, **47**, 397 (1926).